Diabetes and obesity are significant risk factors for morning hypertension: From Ibaraki Hypertension Assessment Trial (I-HAT)

Masahiro Toyama[a], Shigeyuki Watanabe[a], Takashi Miyauchi[b], Yasuhisa Kuroda[a], Eiji Ojima[a], Akira Sato[b], Yoshihiro Seo[b], Kazutaka Aonuma[b]

[a]Mito Kyodo Hospital, Tsukuba University Hospital Mito Medical Center

[b]Graduate School of Comprehensive Human Science, University of Tsukuba

Correspondence to: Shigeyuki Watanabe

Department of Cardiology, Tsukuba University Hospital Mito Medical Center

3-2-7 Miyamachi, Mito, Ibaraki, 301-0015, Japan

Tel: +81 29 231 2371; Fax: +81 29 221 5137

E-mail: watanabe.s.gn@u.tsukuba.ac.jp

Word count: Abstracts, 215 words; Introduction, 297 words; Discussion, 876 words; Conclusion, 29 words

Figure/table count: 2 figures, 5 tables

This work was presented at the Thirteenth International Conference on Endothelin (held at the University of Tsukuba, Tokyo Campus: September 8 - 11, 2013), and was published as an abstract form in the Program and Abstract Book (Cross Border Session PC-15 : 2013) of this Meeting.

Abstract

Aims: Morning hypertension (HT) has been identified as a major cardiovascular risk factor, but the population susceptible to morning HT is unknown. This study aimed to clarify the relationship between morning HT and diabetes or obesity in a large-scale population.

Main methods: Clinic blood pressure (BP) and the BP upon awakening of 2554 outpatients with HT who attended 101 clinics or hospitals, were recorded for two weeks. Hypertension was defined as mean clinic BP > 140/90 mmHg or awakening BP >135/85 mmHg. The patients were assigned to 4 groups (normal BP, white coat HT, masked HT, and sustained HT) based on values of clinic and home BPs.

Key findings: Morning BP (mmHg) was significantly elevated and progressed in the order of

normal glucose tolerance, impaired glucose tolerance and diabetes (134.1 ± 12.2, 135.4 ± 13.1 and 137.5 ± 11.5, respectively; $p < 0.0001$). The incidence of morning HT significantly increased in the same order (53.4%, 55.6%, 66.4%, respectively, $p < 0.0001$). Morning BP was significantly higher among obese diabetic, than non-obese and non-diabetic patients (138.8 ± 10.5, 133.1 ± 11.9, $p < 0.0001$). The incidence of morning HT was also significantly higher in obese diabetic patients than in non-obese and non-diabetic patients (73.0% vs. 49.9%, $p < 0.0001$).

Significance: Morning HT frequently occurs in diabetic or obese patients.

Key words: morning hypertension, masked hypertension, home blood pressure measurement, diabetes, obesity, cardiovascular risk, endothelin

Abstract

Aims Although morning hypertension (HT) has been identified as a major cardiovascular risk, susceptible populations remain unknown. This study aimed to clarify the relationship between morning HT and diabetes or obesity in a large-scale population.

Main methods Clinic blood pressure (BP) and BP upon awakening were recorded in 2554 outpatients with HT who attended 101 clinics or hospitals for two weeks. Mean clinic and awakening BP > 140/90 and >135/85 mmHg, respectively, were considered as HT. The patients were classified according to values for clinic and home BP, into normal BP, white coat HT, masked HT, and sustained HT.

Key findings Morning BP (mmHg) significantly and progressively elevated in the order of normal glucose tolerance, impaired glucose tolerance and diabetes (134.1 ± 12.2, 135.4 ± 13.1 and 137.5 ± 11.5; $p < 0.0001$). The incidence of morning HT significantly increased and progressively in the same order (53.4%, 55.6%, 66.4%, $p < 0.0001$). Morning BP was significantly higher among obese patients with diabetes than among non-obese and non-diabetic patients (138.8 ± 10.5, 133.1 ± 11.9, $p < 0.0001$). In addition, the incidence of morning HT was significantly higher in obese diabetic patients than in non-obese and

non-diabetic patients (73.0% vs. 49.9%, $p < 0.0001$).

Significance Diabetic or obese patients frequently have morning HT.

Introduction

Hypertension (HT) is a globally important lifestyle-related disease that is closely associated with cardiovascular disease (CVD) and thus, blood pressure (BP) should be intensively controlled. Such control requires reliable BP measurement. One study has indicated some limitations of control based on clinic BP [1]. Self-measurement of BP at home is reliable and it is widely recognized as a useful clinical tool. Home, but not clinic BP is a powerful predictor of CVD and elevated home BP is a major cardiovascular risk factor [2]. Several recent guidelines recommend controlling BP throughout a 24-hour period [3-5].

One problem of BP control based on clinic BP is masked HT, which is defined as elevated blood pressure at home or during ambulatory blood pressure monitoring despite normal clinic blood pressure values. The incidence of cardiovascular events is similar between patients with masked and sustained HT and higher than in those with white coat HT and true normal BP [6]. As cardiovascular events often occur during the morning, masked HT, especially in the

morning is a very important risk factor for CVD [7]. On the other hand, white coat HT in which BP is high only while being measured at clinics, is not associated with increased cardiovascular risk, and usually does not require medication.

Diabetes mellitus (DM) and obesity are important lifestyle-related diseases that comprise the most important risk factors for CVD. The most current guidelines of the Japanese Society of Hypertension (JSH2009) recommend very strict BP control with a target blood pressure < 130/80 mmHg in patients with diabetes. However, which populations are susceptible to morning HT, and the characteristics of BP in patients with DM or obesity have not been elucidated. The present study aimed to clarify the relationship between morning HT and diabetes or obesity in a large-scale population.

Material and methods

Study design

The Ibaraki Hypertension Assessment Trial (I-HAT) evaluated blood pressure (BP) control in patients with hypertension. This multicenter cross-sectional study included 101 clinics and hospitals in Ibaraki Prefecture, Japan. Patients who satisfied the following criteria were

recruited by general physicians and hospital-based cardiologists: under treatment for essential HT defined by their attending physicians, clinic BP values > 140/90 mmHg on two separate occasions and patients who could measure their BP upon awakening at home for two weeks. Home and clinic BP, demographics and medical information including age, sex, body mass index (BMI), diabetes mellitus (DM) or impaired glucose tolerance (IGT), estimated glomerular filtration ratio (eGFR), chronic kidney disease (CKD) and a history of cardiovascular events (myocardial infarction, angina pectoris) were collected in case report forms between October 2008 and March 2009. The study proceeded according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, and our institutional review board approved the study protocol.

Home BP measurements

The patients measured their home BP every morning using electrical self-measurement arm-cuff devices based on the cuff-oscillometric method according to the Japanese guidelines for home BP measurements. Awakening BP was measured while seated, within 1 hour of awakening and after > 2 minutes of rest, but before drug ingestion and breakfast. All

measurements were continuously recorded for two weeks. The means of all measurements for each patient were analyzed.

Clinic BP measurements

Clinic BP was measured twice at each regularly scheduled visit, before and after the two weeks of home BP measurement. Blood pressure was measured while seated after resting for at least 2 minutes. The means of all clinic BP values for each patient were analyzed.

Classification of patients

The patients were classified based on the following: home BP values at awakening, clinic BP values as having normal BP (clinic and home BP < 140/90 and < 135/85 mmHg, respectively); white coat HT (clinic and home BP ≥ 140/90 and < 135/85 mmHg, respectively); masked HT (clinic and home BP < 140/90 m and ≥ 135/85 mmHg, respectively) and sustained HT (clinic and home BP ≥ 140/90 and ≥ 135/85 mmHg, respectively). Masked HT plus sustained HT were considered as morning HT.

DM was diagnosed by any of the followings: fasting plasma glucose level ≥ 126 mg/dl, plasma glucose ≥ 200 mg/dl 2 hours after a 75g oral glucose load or casual plasma glucose ≥ 200 mg/dl. Patients with fasting glucose levels from 110 to 125 mg/dl, or plasma glucose ≥ 140 mg/dl, but not ≥ 200 mg/dl 2 hours after a 75 g oral glucose load are considered to have IGT. Obesity was defined as BMI ≥ 25 kg/m^2 according to the definition of Japan Society for the Study of Obesity (JASSO). According to glucose tolerance and obesity, the patients were divided into groups with non-obese normal glucose tolerance (NGT), obese NGT, non-obese DM and obese DM. Because the number of the patients with impaired glucose tolerance (IGT) was small (n=90), we excluded IGT cases in this subdivisional analysis.

Data collection and statistical analysis

Information about patient characteristics and home BP and clinic BP values were collected by a questionnaire administered by an attending physician. All values are expressed as means ± SD. Associations between home/clinic BP and each glucose tolerance group or obese-diabetic group were examined using ANOVA. Post-hoc Bonferroni/Dunn correction was applied. Categorical variables between groups were compared using the chi-squared test. P values <

0.05 were considered significant. All data were statistically analyzed using Stat View 5.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patients

Among 2554 outpatients, we excluded 51 who measured their clinic BP only once during the observation period. Because 395 individuals had no records of body weight or height, their BMI could not be calculated and thus, the presence or absence of obesity remained undetermined, and they were excluded from the present analysis. Therefore, data from 2108 patients were analyzed. Table 1 shows the clinical characteristics of the patients. The mean age of the 2108 patients was 66.7 ± 10.5 years, 46.5% were male and 50.8% were female (in 2.7%, gender undetermined), 837 (39.7%) were obese, 422 (20.0%) had DM, 90 (4.3%) had IGT and the remaining 1596 (75.7%) had NGT. A history of MI, angina pectoris, or hypercholesterolemia was identified in 59 (2.8%), 93 (4.4%) and 694 (32.9%) patients, respectively.

Associations between home/clinic BP and glucose tolerance

Clinic systolic BP did not significantly differ among patients with NGT, IGT or DM (Table 2). However, awakening systolic BP significantly increased as glucose tolerance worsened (NGT, IGT and DM: 134.1 ± 12.2, 135.4 ± 13.1 and 137.5 ± 11.5, respectively; $p < 0.0001$). The frequencies of masked (28.8%, 33.3% and 38.2%, respectively) and sustained (24.6%, 22.2% and 28.2%, respectively) HT similarly increased. Figure 1 shows that morning HT significantly increased with worsening glucose tolerance (53.4%, 55.6% and 66.4%, respectively; $p < 0.0001$).

Table 3 shows the characteristics of patients with NGT, IGT and DM. The ratio of males significantly increased with worsening glucose tolerance (NGT, IGT and DM: 44.7%, 50.6% and 58.8%, respectively; $p < 0.0001$) and BMI also progressed in the same order (24.1, 24.5 and 24.9, respectively; $p < 0.0001$). However, age and eGFR were similar among the three groups. Moreover, the number of antihypertensive drugs administered per patient did not significantly differ among the groups.

Associations between home/clinic BP and DM and obesity

Table 4 shows that clinic BP significantly differed among the four groups ($p = 0.0029$). The clinic SBP tended to be lower among non-obese patients with NGT than the others. Awakening BP significantly increased in the order of non-obese NGT, obese NGT, non-obese DM and obese DM (133.1 ± 11.9, 135.6 ± 12.5, 136.4 ± 12.3 and 138.8 ± 10.5, respectively, $p < 0.0001$). The frequencies of masked (26.9%, 31.8%, 34.7% and 42.0%, respectively) and sustained (23.0%, 27.4%, 25.7% and 31.0%, respectively; $p < 0.0001$) HT similarly increased. Figure 2 shows that the incidence of morning HT significantly increased in the same order (49.9%, 59.3%, 60.4% and 73%; $p < 0.0001$). Morning HT was most frequent among obese patients with DM.

Table 5 shows the characteristics of the four groups. Significantly more male patients had DM than NGT. However, eGFR and the number of antihypertensive drugs administered per patient did not significantly differ among the groups. The obese group with DM was the youngest despite having the highest BP.

Discussion

The present study found no significant differences in clinic BP values among the glucose tolerance groups, but the awakening BP values measured at home significantly increased as glucose tolerance worsened. Therefore, the rate of morning HT increased in accordance with glucose tolerance to 67% in patients with DM. More importantly, the frequency of morning HT increased to 73% when accompanied by obesity.

Clinical significance of morning HT for cardiovascular events

Adverse cardiovascular events such as myocardial infarction [8-10], stroke [11,12] and sudden cardiac death [10,13,14] often occur during the morning. Several studies have shown that morning HT is a cardiovascular risk. The Ohasama study [1] compared home BP measured every morning for four weeks and prognosis in a 6.6-year follow-up of 1789 Japanese rural community dwellers. That study was the first to validate the prognostic significance of home BP measurements as it found that self-measured home BP was significantly and closely related to cardiovascular mortality risk. Another study of the predictive power of self-measured blood pressure at home among 1766 individuals found that both morning and evening BP provided

useful information for stroke risk evaluation, whereas morning HT might specifically be a good predictor of stroke [15]. Kario and colleagues also found that morning HT was the most powerful predictor of stroke among elderly hypertensive patients [16].

Mechanisms of morning HT

Chronic kidney disease [17], left ventricular hypertrophy [18] and atherosclerosis [19] are associated with morning HT. The precise mechanisms of morning HT are unclear. Neurohumoral factors and the salt-sensitivity of BP are thought to be very important. The activities of neurohumoral factors, such as the sympathetic nervous and renin-angiotensin systems increase in the morning, and these might partly contribute to morning HT. Increased sympathetic nerve activity, particularly the alpha-adrenergic component, increases vascular tone in resistant arteries [20]. Sympathetic nerve activity is also affected by a high-salt diet in salt-sensitive patients, in whom BP does not fall during the night [21] and nocturnal BP profiles are affected by sodium intake [22]. An excess circulation volume, autonomic and sleep

disturbances reportedly cause nocturnal BP not to decrease or increase (night BP non-dippers or risers), followed by morning HT. Excess intravascular fluid might be caused by CKD, congestive heart failure and salt-sensitivity.

From the viewpoint of medication, high morning BP might be partly mediated by a short duration of antihypertensive drug action [23].

Mechanisms of morning HT in patients with diabetes and obesity

Hypertension in patients with non-insulin-dependent DM is frequently salt-sensitive, which might be due to sodium retention and enhanced vascular reactivity [24]. Patients with both diabetes and obesity are commonly insulin resistant and insulin resistance is closely associated with the salt-sensitivity of BP [25,26]. Hyperinsulinemia induced by insulin resistance, increases renal tubular sodium reabsorption [27]. Increased salt intake causes excess volume expansion in salt-sensitive patients. In addition, patients with DM are frequently complicated with autonomic nerve disturbances. Orthostatic hypotension and diurnal hypotension caused by autonomic nerve disturbance decrease renal blood flow, resulting in a decrease in urinary

volume and excess body fluid, which causes nocturnal and morning HT. Sleep disturbances that are quite common in obese patients, increase sympathetic nerve activity that also appears to play important roles in sodium and water retention. Uzu et al. reported that diuretics shift the circadian rhythms of BP from non-dipper to dippers in patients with essential HT [28]. However, because of their adverse effects on serum electrodes and glucose tolerance, potassium-sparing diuretics are significantly less frequently administered to hypertensive patients with diabetes or obesity [29]. This seems to be one important reason why diabetic and obese patients with morning HT have persistently uncontrolled BP and a poor cardiovascular prognosis.

Perspectives

Treatment-resistant hypertension often represents morning hypertension. Subjects with treatment-resistant hypertension are at a greater risk for stroke, renal insufficiency, and cardiovascular events. For improving the prognosis of the patients with treatment-resistant hypertension, the clinical development of new class of antihypertensive drug is desired. A new class of antihypertensive drug such as an endothelin receptor antagonist has been reported to effective in patients with treatment-resistant hypertension[30,31]. It has also been reported that

diabetes mellitus and chronic kidney diseases often cause treatment-resistant hypertension and that an endothelin antagonist has been reported to effective in patients with diabetic nephropathy [32]. It also has been reported that the plasma level of endothelin was increased in patients with essential hypertension [33]. These reports provide an argument that a new class of antihypertensive drug with blocking neurohumoral factors is needed to treat morning hypertension and that an endothelin antagonist may become a new drug for morning hypertension.

Study limitations

The present study has some limitations. Firstly, the cross-sectional, observational I-HAT study was implemented during one time-point in a single Japanese prefecture during the cold season (October to March) when BP tends to increase in patients with HT. Secondly, no information about drug compliance and life-styles, including food and alcohol consumption, were available. Poor drug compliance is an important cause of resistant HT. Thirdly, the patients recorded their own home BP values on work sheets and thus, some degree of bias in the recorded BP values cannot be ruled out. Finally, there must be some biases or modification in classifying patients

into white coat, masked, or sustained hypertension, because most patients are already under medical treatment.

Conclusion

The I-HAT study showed that morning HT was more frequent among diabetic or obese hypertensive treated patients. Physicians should treat HT more intensively to achieve home awakening BP targets.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Funding sources

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (24590654).

Acknowledgments

We thank the following physicians who participated in the I-HAT study and made this work possible.

I-HAT investigators:

A Miyamoto, A Atsumi, A Katoh, A Imamura, A Yamazaki, A Goto, B Niho, D Abe, F Kamezaki, F Makabe, H Nakagawa, H Kobayashi, H Asakura, H Unno, H Kikuchi, H Nakajima, H Torigoe, H Tanaka, H Ebata, I Hanyuu, J Miyamoto, J Munakata, K Matsumaru, K Goshima, K Ishii, K Frushou, K Sugiura, K Narushima, K Taya, K Kawashima, M Kenmochi, M Yamaki, M Kaneko, M Endo, M Katou, M Komatsuzaki, M Sonobe, M Saitou, M Kanou, M Kobayashi, M Mizutani, M Ishii, M Ogura, M Kenjou, M Sasaki, M Noritake, M Itou, M Satoh, M Tokoi, M Miyazaki, M Hiyama, M Kuno, M Kumagae, N Maeda, N Murakoshi, N Yamaguchi, N Matsukura, N Takeyasu, R Yamada, R Tachieda, R Sugaya, R Kawakami, S Ebata, S Abeta, S Satou, S Watanabe, S Nemoto, S Suzuki, S Yamaguchi, S Gotou, T Morimoto, T Watanabe, T Kurosawa, T Saitou, T Ayabe, T Yodonawa, T Koh, T Kasano, T Ohkubo, T Ishizu, T Nagano, T Kaizan, T Kawamoto, T Inaba, T Murata, T Tasaki, T Aoki, T Enomoto, W Njaman, Y Ishii, Y Iwamoto, Y Shimizu, Y Takagi, Y Kusama, Y Seo, Y Obara, Y Itou, Y Handa, Y Shiraishi, Y Watanabe, Y Azami, Y Arita, Y Saitou, Y Shimizu, Y Watanabe, and Y

Hatagawa.

References

[1] Ohkubo T, Imai Y, Tsuji I, Nagai K, Katoh J, Kikuchi N, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens 1998; 16: 971-5.

[2] Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, et al. Cardiovascular prognosis of "Masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004; 291: 1342-9.

[3] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42: 1206-52.

[4] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European society of hypertension(ESH) and of the European society of cardiology(ESC). Eur Heart J 2007; 28: 1462-536.

[5] Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al. The Japanese

society of hypertension guidelines for the management of hypertension (JSH2009). Hypertens Res 2009; 32: 3-107.

[6] Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens 2007; 25: 2193-8.

[7] Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003; 107: 1401-6.

[8] Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313: 1315-22.

[9] Tofler GH, Muller JE, Stone PH, Forman S, Solomon RE, Knatterud GL, et al. Modifiers of timing and possible triggers of acute myocardial infarction in the Thrombolysis in Myocardial infarction phase II (TIMI II) study Group. J Am Coll Cardiol 1992; 20: 1049-55.

[10] Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997; 79: 1512-6.

[11] Mackey J, Kleindorfer D, Sucharew H, Moomaw CJ, Kissela BM, Alwell K, et al. Population-based study of wake-up strokes. Neurology 2011; 76: 1662-7.

[12] Turin TC, Kita Y, Rumana N, Takashima N, Ichikawa M, Sugihara H, et al. Morning surge in circadian periodicity of ischaemic stroke is independent of conventional risk factor status: findings from the Takashima Stroke Registry 1990-2003. Eur J Neurol 2009; 16: 843-51.

[13] Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987; 75: 131-8.

[14] Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am J Cardiol 1987; 60: 801-6.

[15] Asayama K, Ohkubo T, Kikuya M, Obara T, Metoki H, Inoue R, et al. Prediction of stroke by home “morning” versus “evening” blood pressure values: the Ohasama study.

Hypertension 2006; 48: 737-43.

[16] Kario K, Ishikawa J, Pickering TG, Hoshide S, Eguchi K, Morinari M, et al. Morning hypertension: the strongest independent risk factor for stroke in elderly hypertensive patients. Hypertens Res 2006: 29: 581-7.

[17] Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. Diabetes Care 2002; 25: 2218-23.

[18] Ikeda T, Gomi T, Shibuya Y, Matsuo K, Kosugi T, Oku N, et al. Morning rise in blood pressure is a predictor of left ventricular hypertrophy in treated hypertensive patients. Hypertens Res 2004; 27: 939-46.

[19] Marfella R, Siniscalchi M, Nappo F, Gualdiero P, Esposito K, Sasso FC, et al. Regression of carotid atherosclerosis by control of morning blood pressure peak in newly diagnosed hypertensive patients. Am J Hypertens 2005; 18: 308-18.

[20] Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to α-sympathetic vasoconstrictor activity. N Engl J Med 1991; 325: 986-90.

[21] Okuguchi T, Osanai T, Kamada T, Kimura M, Takahashi K, Okumura K. Significance of sympathetic nervous system in sodium-induced nocturnal hypertension. J Hypertens 1999; 17: 947-57.

[22] Sica DA. What are the influences of salt, potassium, the sympathetic nervous system, and the renin-angiotensin system on the circadian variation in blood pressure? Blood Press Monit 1999; 4(suppl 2): S9-16.

[23] Chonan K, Hashimoto J, Ohkubo T, Tsuji I, Nagai K, Kikuya M, et al. Insufficient duration of action of antihypertensive drugs mediates high blood pressure in the morning in hypertensive population: the Ohasama study. Clin Exp Hypertens 2002; 24: 261-75.

[24] Tuck M, Corry D, Trujillo A. Salt-sensitive blood pressure and exaggerated vascular reactivity in the hypertension of diabetes mellitus. Am J Med 1990; 88:210-6.

[25] Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989; 321: 580-5.

[26] Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, Araki S, et al. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens 2006; 24: 1627-32.

[27] Rocchini AP. The relationship of sodium sensitivity to insulin resistance. Am J Med Sci 1994; 307(Suppl 1): S75-80.

[28] Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. Circulation 1999; 100:1635-8.

[29] Ohira T, Tanigawa T, Tabata M, Imano H, Kitamura A, Kiyama M, et al. Effects of habitual alcohol intake on ambulatory blood pressure, heart rate, and its variability among Japanese men. Hypertension 2009; 53: 13-9.

[30] Dhaun N, Johnston NR, Goddard J, Webb DJ. Chronic selective endothelin A receptor antagonism reduces serum uric acid in hypertensive chronic kidney disease. Hypertension 2011; 58: e11-2.

[31] Moorhouse RC, Webb DJ, Kluth DC, Dhaun N. Endothelin antagonism and its role in the treatment of hypertension. Curr Hypertens Rep 2013; 15: 489-96.

[32] Andress DL, Coll B, Pritchett Y, Brennan J, Molitch M, Kohan DE. Clinical efficacy of the selective endothelin A receptor antagonist, atrasentan, in patients with diabetes and chronic kidney disease (CKD). Life Sci. 2012; 15: 739-42.

[33] Saito Y, Nakao K, Mukoyama M, Imura H. Increased plasma endothelin level in patients with essential hypertension. N Engl J Med 1990; 322: 205.

Table 1. Patients' characteristics (n = 2108).

Characteristics	
Age (y)	66.7 ± 10.5
Male / Female (n%)*	981 (46.5%) / 1071 (50.8%)
BMI (kg/m^2)	24.3 ± 3.3
eGFR (mL/min/1.73 m^2)†	72.2 ± 18.6
Diabetes (n%)	422 (20.0%)
Impaired glucose tolerance (n%)	90 (4.3%)
Obesity (n%)	837 (39.7%)
History of effort angina (n%)	93 (4.4%)
History of myocardial infarction (n%)	59 (2.8%)
Chronic kidney disease (n%)†	527 (34.0%)
Hyperlipidemia (n%)	694 (32.9%)
Antihypertensive medication	
Number of drugs, mean (n)	1.8 ± 0.9
0 (n %)	51 (2.4%)
1 (n %)	768 (36.4%)
2 (n %)	881 (41.8%)
3 (n %)	301 (14.3%)
≥ 4 (n %)	107 (5.1%)
Drug classes including combinations (n%)	
Ca channel blockers	1 355 (64.3%)
Angiotensin converting enzyme inhibitor s	156 (7.4%)
Angiotensin II receptor blockers	1 588 (75.3%)
α-blockers	101 (4.8%)
β-blockers	312 (14.8%)
Diuretics	337 (16.0%)

Values are expressed as means ± standard deviation of mean (SD) for continuous variables. BMI, Body mass index; eGFR, estimated glomerular filtration rate. *Sex unknown (n = 56) . †Information about eGFR and CKD unavailable (n = 556).

Table 2. Comparison of clinic BP and home BP upon awakening according to glucose tolerance.

	NGT	IGT	DM	p value
n	1 596	90	422	
Clinic SBP (mmHg)	135.9 ± 13.7	136.8 ± 15.3	137.4 ± 13.4	NS
Clinic DBP (mmHg)	76.9 ± 10.9	76.3 ± 10.6	77.0 ± 10.8	NS
Awakening SBP (mmHg)	134.1 ± 12.2	135.4 ± 13.1	137.5 ± 11.5	<0.0001
Awakening DBP (mmHg)	78.5 ± 9.5	78.6 ± 9.9	78.5 ± 9.3	NS
Normal BP (%)	32.7%	32.2%	23.9%	0.0004
White coat HT (%)	13.9%	12.2%	9.7%	
Masked HT (%)	28.8%	33.3%	38.2%	
Sustained HT (%)	24.6%	22.2%	28.2%	

Values are expressed as means ± standard deviation of means (SD) for continuous variables. DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NS, non-significant; SBP, systolic blood pressure.

Table 3. Characteristics of patients with NGT, IGT and DM.

	NGT	IGT	DM	p value
n (%)	1 596 (75.8%)	90 (4.3%)	422 (20.0%)	
Age (y)	66.7 ± 10.6	66.1 ± 9.2	66.7 ± 10.5	NS
Male (%)*	44.7%	50.6%	58.8%	<0.0001
BMI (kg/m^2)	24.1 ± 3.3	24.5 ± 3.2	24.9 ± 3.5	<0.0001
eGFR (mL/min/1.73 m^2)†	72.3 ± 18.2	71.7 ± 16.3	72.3 ± 20.5	NS
Obesity (n%)	594 (37.2%)	43 (47.8%)	200 (47.4%)	0.0002
History of effort angina (n%)	60 (5.9%)	8 (8.9%)	25 (5.9%)	0.0168
History of myocardial infarction (n%)	35 (2.2%)	5 (5.6%)	19 (4.5%)	0.0102
Chronic kidney disease (n%)†	366 (32.9%)	24 (34.3%)	137 (36.9%)	NS
Antihypertensive medication				
Number of drugs, mean (n)	1.8 ± 0.9	1.9 ± 1.0	1.9 ± 1.0	NS
0 (n%)	40 (2.5%)	4 (4.4%)	7 (1.7%)	
1 (n%)	587 (36.8%)	27 (30.0%)	154 (36.5%)	
2 (n%)	667 (41.8%)	42 (46.7%)	172 (40.8%)	
3 (n%)	231 (14.5%)	11 (12.2%)	59 (14.0%)	
≥ 4 (n%)	71 (4.4%)	6 (6.7%)	30 (7.1%)	
Class of drugs (including combinations)				
Ca channel blockers (n%)	1 022 (64.0%)	69 (76.7%)	264 (62.6%)	0.0369
Angiotensin converting enzyme inhibitor (n%)	110 (6.9%)	9 (10.0%)	37 (8.8%)	NS
Angiotensin II receptor blocker (n%)	1 185 (74.2%)	66 (73.3%)	337 (79.9%)	NS
α-blockers (n%)	77 (4.8%)	1 (1.1%)	23 (5.5%)	NS
β-blockers (n%)	236 (14.8%)	12 (13.3%)	64 (15.2%)	NS
Diuretics (n%)	256 (16.0%)	12 (13.3%)	69 (16.4%)	NS

Values are expressed as means ± standard deviation of mean (SD) for continuous variables. BMI, Body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; NS, non-significant. *Sex unknown (n = 56). †Information about eGFR and chronic kidney disease unavailable (n = 556).

Table 4. Comparison of clinic BP and home BP upon awakening according to glucose tolerance and obesity.

	NGT		DM		
	Non-obese	Obese	Non-obese	Obese	p value
n	1 002	594	222	200	
Clinic SBP (mmHg)	135.1 ± 13.9	137.3 ± 13.4	137.5 ± 13.6	137.3 ± 13.1	0.0029
Clinic DBP (mmHg)	76.2 ± 10.9	78.0 ± 11.0	75.6 ± 10.6	78.4 ± 10.9	0.0007
Awakening SBP (mmHg)	133.1 ± 11.9	135.6 ± 12.5	136.4 ± 12.3	138.8 ± 10.5	<0.0001
Awakening DBP (mmHg)	77.5 ± 9.1	80.3 ± 9.8	76.0 ± 9.2	81.2 ± 8.6	<0.0001
Normal BP (%)	36.7%	25.9%	26.6%	21.0%	
White coat HT (%)	13.4%	14.8%	13.1%	6.0%	<0.0001
Masked HT (%)	26.9%	31.8%	34.7%	42.0%	
Sustained HT (%)	23.0%	27.4%	25.7%	31.0%	

Values are expressed as means ± standard deviation of mean (SD) for continuous variables. DM, diabetes mellitus; NGT, normal glucose tolerance; NS, non-significant; SBP, systolic blood pressure; SBP, systolic blood pressure.

Table 5. Characteristics of patients with and without obesity and different glucose tolerance.

	NGT		DM		
	Non-obese	Obese	Non-obese	Obese	p value
n (%)	1 002 (49.7%)	594 (29.4%)	222 (11.0%)	200 (9.9%)	
Age (y)	67.8 ± 10.0	65.1 ± 11.4	68.9 ± 9.8	64.2 ± 10.6	<0.0001
Male (%)	43.6%	46.6%	60.3%	57.1%	<0.0001
BMI (kg/m^2)	22.2 ± 1.9	27.4 ± 2.5	22.4 ± 1.9	27.7 ± 2.5	<0.0001
eGFR (mL/min./1.73 m^2)	72.3 ± 17.8	72.3 ± 18.8	70.5 ± 20.3	74.3 ± 20.6	NS
History of effort angina (n%)	47 (4.7%)	13 (2.2%)	17 (7.7%)	8 (4.0%)	0.0043
History of myocardial infarction (n%)	26 (2.6%)	9 (1.5%)	13 (5.9%)	6 (3.0%)	0.0081
Chronic kidney disease (n%)	214 (31.7%)	152 (34.9%)	82 (42.1%)	55 (31.3%)	0.0449
Antihypertensive medication					
Number of drugs, mean (n)	1.8 ± 0.9	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 1.0	NS
0 (n%)	27 (2.7%)	13 (2.2%)	5 (2.3%)	2 (1.0%)	
1 (n%)	404 (40.3%)	183 (30.8%)	78 (35.1%)	76 (38.0%)	
2 (n%)	403 (40.2%)	264 (44.4%)	94 (42.3%)	78 (39.0%)	
3 (n%)	132 (13.2%)	99 (16.7%)	29 (13.1%)	30 (15.0%)	
≥ 4 (n%)	36 (3.6%)	35 (5.9%)	16 (7.2%)	14 (7.0%)	
Class of drugs (including combination therapy)					
Ca channel blocker (n%)	626 (62.5%)	396 (66.7%)	139 (62.6%)	125 (62.5%)	NS
Angiotensin converting enzyme inhibitor (n%)	75 (7.5%)	35 (5.9%)	24 (10.8%)	13 (6.5%)	NS
Angiotensin II receptor blockers (n%)	718 (71.7%)	467 (78.6%)	170 (76.6%)	167 (83.5%)	0.0004
α-blockers (n%)	45 (4.5%)	32 (5.4%)	14 (6.3%)	9 (4.5%)	NS
β-blockers (n%)	142 (14.2%)	94 (15.8%)	36 (16.2%)	28 (14.0%)	NS
Diuretics (n%)	136 (13.6%)	120 (20.2%)	33 (14.9%)	36 (18.0%)	0.0048

Values are expressed as means ± standard deviation of mean (SD) for continuous variables. BMI, Body mass index; eGFR, estimated glomerular filtration rate; NGT, normal glucose tolerance; DM, diabetes mellitus; NS, non-significant.

Figure Captions.

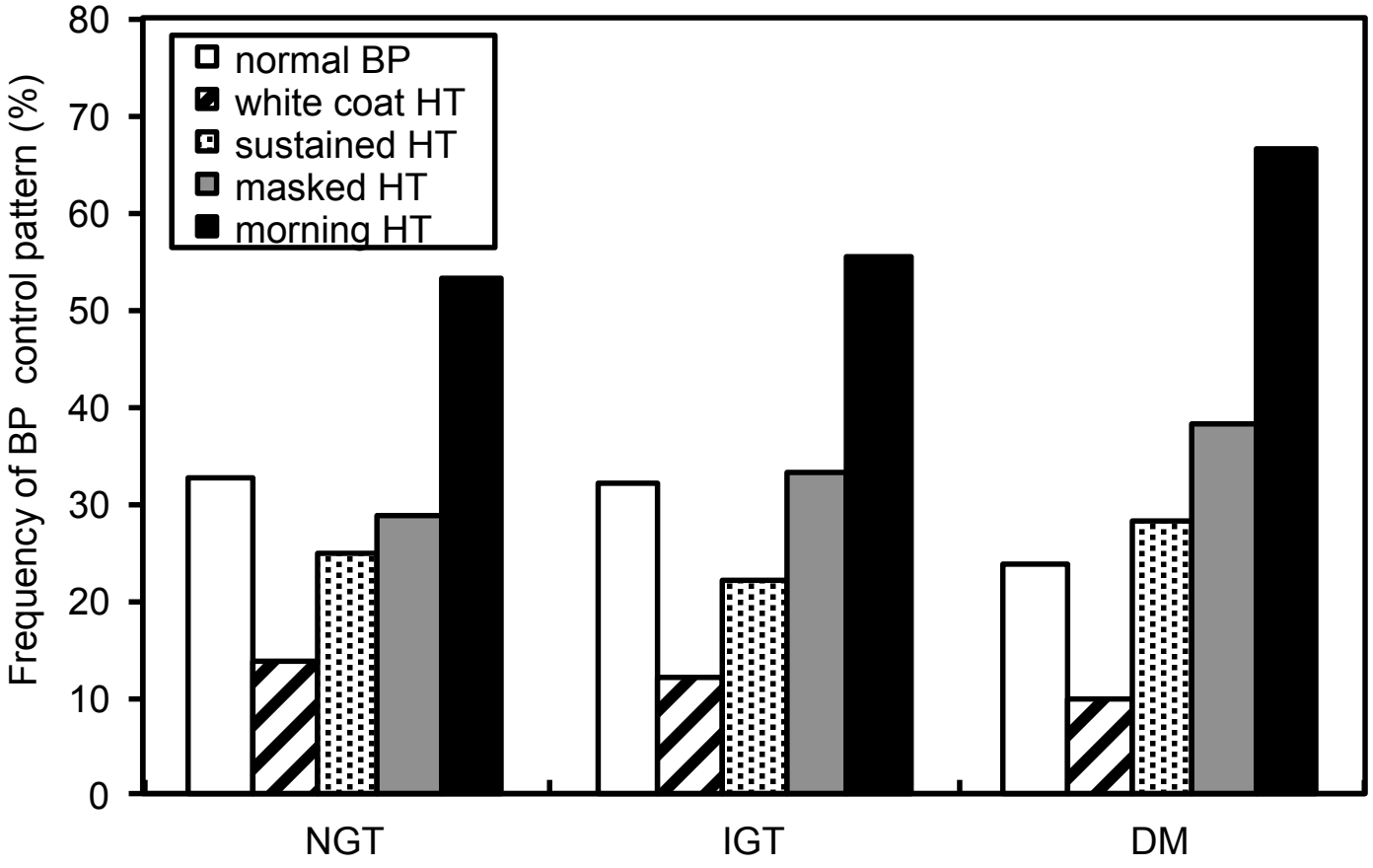
Fig. 1. Frequency of BP control among glucose tolerance groups.

Patients were classified into groups based on awaking home BP and clinic BP. Morning HT comprised masked HT plus sustained HT. Morning HT significantly increased as glucose tolerance worsened (53.4%, 55.6% and 66.4%, respectively; $p < 0.0001$). BP, blood pressure; HT, hypertension; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus.

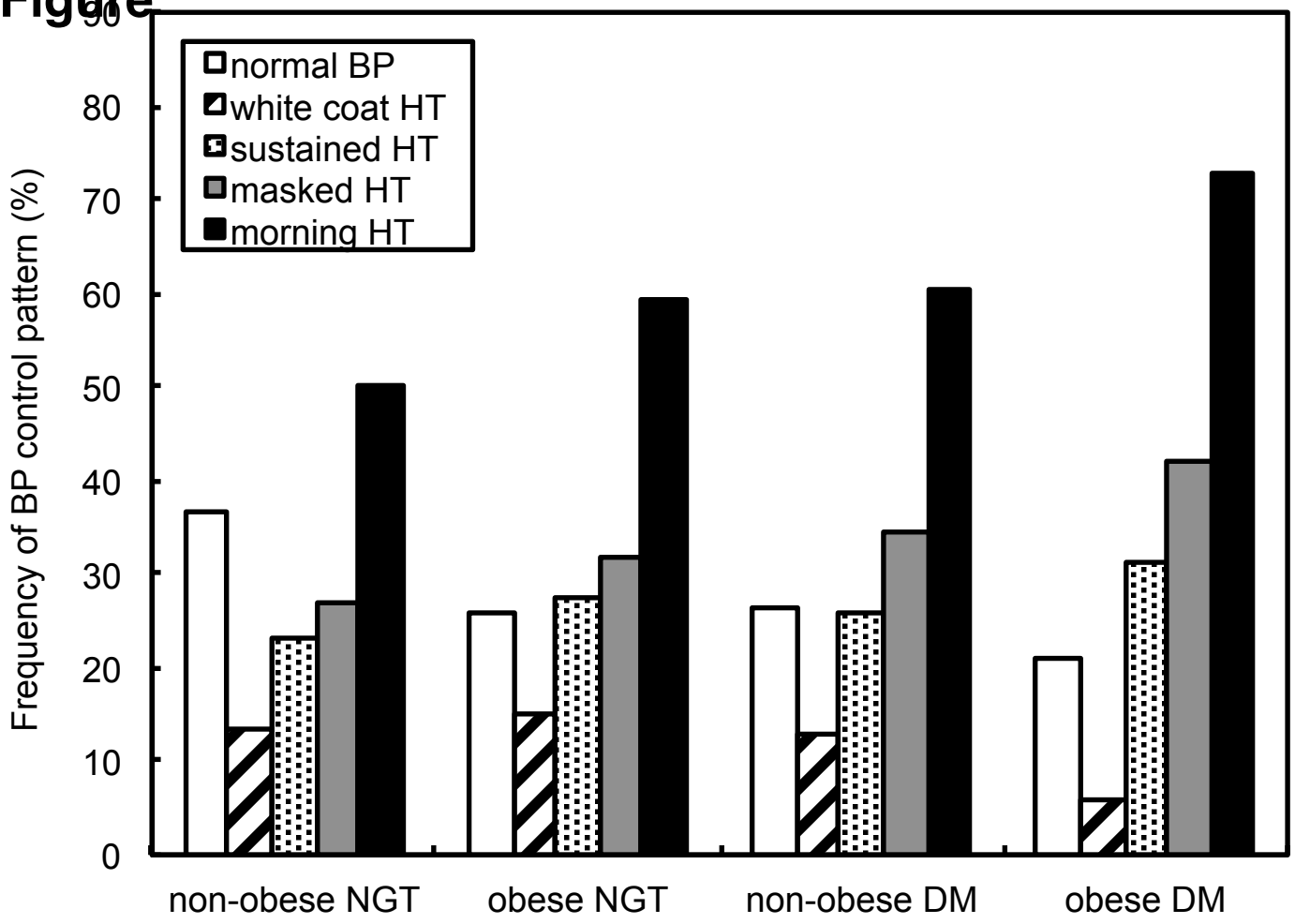
Fig. 2. Frequency of BP control among obese-glucose tolerance groups.

Morning HT significantly increased and progressed in the order of non-obese NGT, obese NTG, non-obese DM and obese DM (49.9%, 59.3%, 60.4% and 73.0%, respectively; $p <0 .0001$). BP, blood pressure; HT, hypertension; NGT, normal glucose tolerance; DM, diabetes mellitus.

Figure


80
70
60
50
40
30
20
10
0
Frequency of BP control pattern (%)
normal BP
white coat HT
sustained HT
masked HT
morning HT
NGT
IGT
DM

Figure


normal BP
white coat HT
sustained HT
masked HT
morning HT
Frequency of BP control pattern (%)
0
10
20
30
40
50
60
70
80
90
non-obese NGT
obese NGT
non-obese DM
obese DM